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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,233	KAYMAKCALAN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,21-24,31,34,35,40-45,48,49,52 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,21-24,31,34,35,40-45,48,49,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed May 7, 2007 is acknowledged.

   Claims 1-14, 18-20, 25-30, 32, 33, 36-39, 46, 47, 50 and 51 have been canceled.

   Claims 15, 21, 31 and 42 have been amended.

   Claims 52 and 53 have been added.

   Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are pending.

   Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are under consideration as they read on a method for treating "rheumatoid arthritis" by administering anti-TNFα antibody.

2. This Office Action is in response to Applicant's amendment and remarks filed May 7, 2007.

   The rejections of record can be found in the previous Office Action, mailed February 8, 2007.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph, written description, has been withdrawn in view of applicant's amendment.

   The previous rejection under 35 U.S.C. § 102(b)/(e) as anticipated by Salfeld have been withdrawn upon further consideration and in view of applicant's argument.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, essentially for the reasons of record.

   The instant claims have been amended to strike the phrase "an effective amount of". Applicant argues this amendment obviates the previous rejection under 35 U.S.C. § 112, 2nd paragraph..

   Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

The instant claims recite "a method of treating arthritis comprising administering to a subject an anti-TNFα antibody...in a low dose of 0.01 – 0.1 mg/kg".

The claims remain indefinite in the recitation of "a low dose of 0.01 – 0.1 mg/kg" because the metes and bounds of this phrase remain unclear.

The instant specification does not define what is meant by "a low dose of 0.01 – 0.1 mg/kg".

In particular, it is unclear if "a low dose of 0.01 – 0.1 mg/kg" is to be read as encompassing only those methods of treatment where the patient is administered a *single* dose of 0.01 – 0.1 mg/kg antibody *and no more*, ***OR*** a method encompassing the administration of *one or more* doses of 0.01 – 0.1 mg/kg antibody to the patient.

If the latter, then administering "a low dose of 0.01 – 0.1 mg/kg" appears to read equally well on, for example:

(a) administering a "low doses of 0.1 mg/kg" *once per minute divided over a 12 minute period* for a total of 1.2 mg/kg anti-TNFα antibody administered, or

(b) administering a "low doses of 0.1 mg/kg" *once per week divided over a 3 month period* for a total of 1.2 mg/kg anti-TNFα antibody administered.

However the metes and bounds of (a) and (b) are different. The instant claims do not define the dosage frequency, and the instant specification does not provide a standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant is reminded that any amendment in response to this rejection must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis with 0.1 mg/kg anti-TNFα antibody, does not reasonably provide enablement for treating rheumatoid arthritis with 0.01 - 0.1 mg/kg anti-TNFα antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims recite "a method of treating arthritis comprising administering to a subject an anti-TNFα antibody...in a low dose of 0.01 – 0.1 mg/kg". However, for the purposes of examination under 35 U.S.C. 112, 1st paragraph, the instant claims are being considered as they read on a dosage of 0.01-0.1 mg/kg at a frequency of not more than once per week, as exemplified by Example 1 on pages 26-30 of the instant specification.

As essentially stated in the prior Office Action, the instant specification discloses the treatment of mice transgenic for TNFα (tg197 mice), which is one model system for rheumatoid arthritis, with two anti-TNFα antibodies, D2E7 and Remicade, including 0.01 mg/kg once per week for 10 weeks.

Neither D2E7 nor Remicade appear to show any consistent effect on arthritic scores when dosed at 0.01 mg/kg once per week for 10 weeks (see, in particular, Example 1, part B and Figures 1, 2 and 4).

Moreover, as a second measure of treatment efficacy, four histopathological features were measured at the end of the 10 week treatment. Again, neither D2E7 nor Remicade appear to be able to elicit an improvement in the measured histological features at the 0.01 mg/kg dose (see, in particular, Example 1, part D and Figure 5).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant argues the instant claims are enabled in view of the data provided in the instant specification and that the specification provides sufficient guidance for one of ordinary skill in the art to practice the claimed method of treatment without undue experimentation.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

MPEP § 2164.08 teaches that "[t]he focus of the examination inquiry is whether everything within the scope of the claim is enabled." However, applicant has not established that the skilled artisan could use a dose of as little as 0.01 mg/kg to treat rheumatoid arthritis in human patients given the data disclosed in the instant specification which demonstrates no consistent effect of treating tg197 mice with 0.01 mg/kg anti-TNFα antibody.

With respect to the data shown in Figure 5, applicant argues that "at the lower range of the claimed dose range, *i.e.*, 0.01 mg/kg, both D2E7 and Remicade showed a positive effect on cartilage erosion, while Remicade showed a positive effect on bone erosion."

Applicant's argument has not been found convincing because there does not appear to be a significant difference between the mean control cartilage erosion and the mean D2E7 cartilage erosion at 0.01 mg/kg based on the significantly overlapping standard deviations surrounding these means (see Figure 5, panel B, first 2 columns left to right).

Moreover, while there may be a significant difference between the mean control cartilage erosion and the mean Remicade cartilage erosion at 0.01 mg/kg, any effect at this low dose is contradicted by the effect of Remicade at 0.1 mg/kg where there is an increase in cartilage erosion versus the control. Thus the effect of Remicade on cartilage erosion is highly unpredictable within the claimed range.

Applicant further argues that Table 2 on page 29 of the specification further demonstrates that anti-TNFα can be used in the claimed range to treat rheumatoid arthritis.

However, it appears that Table 2 was prepared based on the data presented in Figure 5, and thus it shows no more than Figure 5 about practicing the instant claims at the lower limit (0.01 mg/kg) of the claimed dosage range.

Moreover, applicant's argument that (emphasis in the original), "[g]iven that the ED_{50} represents the amount of TNFα antibody required *to affect 50% of the animals,* one of ordinary skill in the art would recognize that a range of doses surrounding the ED_{50} dose would also have a therapeutic effect on a portion of the patient population" is further not convincing because the disclosure of Table 5 that the ED_{50} is approximately $0.01 < ED50 < 0.1$ tells one of ordinary skill in the art no more than that the ED_{50} falls *somewhere* within this range. Without data other than that presented in Figure 5, one of ordinary skill in the art can not predict, a priori, where the ED_{50} value actually occurs, e.g., at 0.095 mg/kg or 0.08 mg/kg, or the breadth of the therapeutically effective range of doses surrounding the ED_{50} dose.

In addition, applicant has failed to address the lack of any consistent effect on arthritic scores when either D2E7 or Remicade anti-TNFα antibodies were dosed at 0.01 mg/kg once per week for 10 weeks as measured by actual physical manifestation of disease rather than by microscopic histopathology (see, in particular, Example 1, part B and Figures 1, 2 and 4).

Applicant further argues that because the instant specification discloses how to analyze the effects of treating mice transgenic for TNFα (tg197 mice) with anti-TNFα antibodies the instant specification discloses, in light of the high level of skill in the art, how to determine concentrations of antibodies that would be effective in treating rheumatoid arthritis.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

Thus, undue experimentation would be required to practice the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In

view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Furthermore, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 15-17 and 21-24 stand rejected under 35 U.S.C. 102(b) as anticipated by Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.)(see entire document), essentially for the reasons of record.

For the purposes of prior art examination the instant claims are being considered as they read on a dosage of 0.01-0.1 mg/kg at a frequency of not more than once per week, as exemplified by Example 1 on pages 26-30 of the instant specification.

As stated in the prior Office Action, Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571. Stephens further teaches that the disease activity measures included tender and swollen joints, and that patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated. Furthermore, all patients receiving CDP571 scored a reduction in pain scale by week 1 (see entire document, in particular pages 326-327).

Applicant acknowledges that Stephens' teaches a clinical study in which rheumatoid arthritis patients were administered a single dose of CDP571 anti-TNFα antibody at 0.1 mg/kg and that disease activity was assessed in these patients at 1, 2, 4 and 8 weeks after infusion (the "first infusion" study described on Stephens page 327).

However, Applicant argues that Stephens does not teach the treatment of rheumatoid arthritis using a dose of 0.1 mg/kg because (emphasis in the original), "Stephens *et al.* provide ***no data*** for the group of patients who received 0.1 mg/kg in either Table 2 or Table 3 and, moreover, ***nowhere in the reference is it disclosed (e.g.,* see, in particular, pages 327-329) *that the dose of 0.1 mg/kg CDP571 had any effect in treating arthritis.***"

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

While tables 2 and 3 of Stephens do not mention the effects of administering 0.1 mg/kg CDP571 anti-TNFα, it is not the case that Stephens fails to disclose "any effect" for the 0.1 mg/kg treatment as can be seen from the following quote:

"First infusion - ***Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment*** with maximum patient responses after 10 mg/kg. After CDP571 10 mg/kg...***All patients who received CDP571 scored a reduction in pain scale by week 1.***" See, Stephens, page 327, 1st paragraph, emphasis added.

The highlighted parts above encompass treatment at *all* doses of CDP571 tested, and they do not exclude 0.1 mg/kg.

Thus, in contrast to applicant's assertion, Stephens teaches treatment of rheumatoid arthritis via administration of all doses tested, including 0.1 mg/kg CDP571 anti-TNFα.

Applicant further asserts that "Stephens *et al.* teach that at the 0.1 mg/kg dose the administered antibody is rapidly cleared," from which applicant draws the conclusion, "Stephens *et al.* expressly teach that the lower dose of 0.1 mg/kg is not effective in treating arthritis, e.g., rheumatoid arthritis, or symptoms associated with arthritis."

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

First of all, applicant's assertion that "Stephens *et al.* teach that at the 0.1 mg/kg dose the administered antibody is rapidly cleared," is not accurate. The teachings of Stephens show that the single dose of 0.1 mg/kg CDP571 anti-TNFα is cleared at approximately the same rate as a single dose at 1 mg/kg or 10 mg/kg as evidenced by the slopes of the lines plotted in the first section of Figure 4.

Moreover, while it is true that Stephens teaches that after an initial dose of 0.1 mg/kg patients "...tended to show a class-switch to IgG anti-CDP571 production...and subsequent doses of CDP471, whether at 1 or 10 mg/kg, boosted specific IgG production, resulting in increased clearance of CDP571," this does ***not*** amount to ***an express teaching that 0.1 mg/kg is not effective*** in treating arthritis as alleged by applicant.

Rather, while Stephens teaches increased CPD571 clearance, and therefore decreased antibody efficacy when patients are treated over particular time periods and at particular dosages, i.e., ***8 weeks after a single administration of 0.1 mg/kg*** CDP571 anti-TNFα there is an increase in anti-CDP571 IgG production, and subsequent doses of CDP571 anti-TNFα antibody ***at 1 or 10 mg/kg resulted in increased CPD571 clearance***, this alone is not sufficient to negate the anticipatory teachings of Stephens. As stated above and in the prior Office Action, Stephens teaches a clinical study involving administration of 0.1 mg/kg anti-TNFα to rheumatoid arthritis patients where disease activity measures included tender and swollen joints, where the anti-TNFα antibody was found to have a dose-dependent effect on all patients treated, and where all of the patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

Lastly, applicant's argument that the absence of a 0.1 mg/kg dose in the second, third and fourth infusions of CDP571 anti-TNFα antibody of the Stephens' teaching "clearly indicates that, indeed, this dose was not effective in treating arthritis, *e.g.*, rheumatoid arthritis, or symptoms associated with arthritis," is utter speculation. Applicant has not provided objective evidence in support of this assertion that Stephens excluded 0.1 mg/kg from the second, third and fourth infusions specifically because it was not effective in treating rheumatoid arthritis.

Thus, Stephens anticipates the instant claims.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 stand rejected and new claims 52-53 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42), essentially for the reasons of record.

For the purposes of prior art examination the instant claims are being considered as they read on a dosage of 0.01-0.1 mg/kg at a frequency of not more than once per week, as exemplified by Example 1 on pages 26-30 of the instant specification.

The teachings of the applied references as put forth in the prior Office Action are summarized as follows:

Stephens teaches ***a clinical study involving administration of 0.1 mg/kg CDP571 anti-TNFα to rheumatoid arthritis patients*** where disease activity measures included tender and swollen joints, where the ***CDP571 anti-TNFα antibody was found to have a dose-dependent effect on all patients treated***, and where all of the patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

While Stephens does not recite administration of fully human anti-TNFα antibody, Salfeld teaches a method of treating rheumatoid arthritis by administering a fully human anti-TNFα antibody, such as D2E7 (see entire document, in particular, e.g. column 4 last paragraph in view of column 3 first paragraph). ***Salfeld further teaches that an effective dose of anti-TNFα antibody is 0.1 – 20 mg/kg, and that the anti-TNFα antibody dosage concentration and frequency is a results effective variable*** that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions" (see, in particular, column 26 1st and 2nd paragraphs). Salfeld also teaches coadministration of various other therapeutic agents along with anti-TNFα antibody (column 23, 2nd paragraph).

Like Salfeld, den Broeder teaches the use of the fully human D2E7 anti-TNFα antibody to treat rheumatoid arthritis patients. In the D2E7 dose titration clinical study of den Broeder, rheumatoid arthritis patients were effectively treated with a 0.25 mg/kg/2-4 weeks of D2E7.

It is noted that conversion of the 0.25 mg/kg dosage of den Broeder to a per week basis gives 0.0625 – 0.125 mg/kg/week, which overlaps the claimed dosage range of 0.01 to 0.1 mg/kg.

Den Broeder further teaches that by using the lowest possible dose of anti-TNFα antibody one can minimize the risk associated with TNFα suppression, such as susceptibility to some infectious disease that would normally be fought off by the proinflammatory activity of TNFα (see entire document, in particular Introduction at paragraph bridging pages 638-639 through, 1st paragraph 639, Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

As set forth in greater detail below in response to applicant's arguments, given the reference teachings it would have been obvious to one of ordinary skill in the art to substitute the D2E7 human anti-TNFα antibody of Salfeld for the CDP571 humanized anti-TNFα antibody of Stephens to treat rheumatoid arthritis patients, for example, at a dose of 0.1 mg/kg/week anti-TNFα antibody.

Applicant argues that the instant claims are not obvious in view of alleged deficiencies in the reference teachings, in view of applicant's alleged "unexpected discovery" that a low dose of 0.01-0.1 mg/kg anti-TNFα antibody can treat arthritis, and in view of the alleged teaching away of Stephens and den Broeder.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

The Stephens Reference

With respect to the Stephens reference, Applicant asserts "Stephens *et al.* basically report that the dose of 0.1 mg/kg was not effective in treating arthritis...Indeed, as noted by the Examiner, Stephens *et al.* disclose that a 0.1 mg/kg dose of CDP571 results in enhanced production of anti-CDP571 antibodies and, as a consequence, *increased clearance of CDP571* from the patient's system, as compared to a higher dose, *e.g.,* 10 mg/kg. Thus, Stephens *et al. teach away* from the claimed invention..."

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

As described in Section 8 above, Stephens does not "basically report that the dose of 0.1 mg/kg was not effective in treating arthritis". Rather, Stephens teaches a clinical trial including a cohort of patients given a single dose at 0.1 mg/kg CDP571 anti-TNFα antibody where, in contrast to the placebo treated patients who did not show improvement, CDP571 anti-TNFα antibody was found to have a dose-dependent effect on the treated patients, and all patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

Moreover, while Stephens does teach increased CPD571 clearance when patients are treated over particular time periods and at particular dosages, i.e., 8 weeks after a single administration of 0.1 mg/kg CDP571 anti-TNFα there is an increase in anti-CDP571 IgG production, and subsequent doses of CDP571 anti-TNFα antibody at 1 or 10 mg/kg resulted in increased CPD571 clearance, this does not negate the other teachings of Stephens that, in contrast to the placebo treatment, treatment with CDP571 anti-TNFα antibody had a dose-dependent effect on the treated patients, and all patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

Thus, while Stephens teaches that under certain limited conditions (which fall within the scope of the instant claims but are certainly not commensurate in scope with the instantly claimed method) the effectiveness of CDP571 anti-TNFα antibody would expected to be compromised, Stephen's nevertheless teaches that treatment of rheumatoid arthritis with 0.1 mg/kg CDP571 anti-TNFα antibody is effective.

Furthermore, the teachings of Salfeld provide a solution to the issue of CDP571 clearance that would be readily recognized by one of ordinary skill in the art.

In particular, one of ordinary skill in the art would have been motivated to substitute the human D2E7 antibody for the humanized CDP571 antibody because, as taught by Salfeld, a fully human antibody, such as D2E7, is preferable to a humanized antibody, such as CDP571, which is 95% human/5% murine, because while humanized antibodies are nearly identical to human antibodies, even a small amount of non-human sequence can elicit an unwanted immune reaction, especially so when administered for long periods as in the treatment of chronic rheumatoid arthritis (see Salfeld, paragraph bridging columns 1-2).

The Salfeld Reference

With respect to the Salfeld reference, applicant acknowledges Salfeld teaches an effective dose of anti-TNFα antibody is 0.1 – 20 mg/kg. However, applicant argues Salfeld fails to teach treatment with a dose of 0.01 - 0.1 mg/kg. Moreover, applicant argues that when considering prior art that touches a claimed range, as in the instant case, "unexpected results" within the claim range may render it obvious. Applicant asserts that the instant specification provides unexpected results.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

Applicant's "unexpected result" is that mice transgenic for TNFα (tg197 mice), which is one model system for rheumatoid arthritis, can allegedly have their arthritis symptoms alleviated with 0.01 – 0.1 mg/kg anti-TNFα antibody. Therefore, applicant alleges human rheumatoid arthritis could also be treated with the same dose.

However, applicant has not established the closest prior art and compared it to their results to establish why their results were unexpected.

"A comparison of the *claimed* invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). See MPEP § 716.02(e).

Nevertheless, assuming that den Broeder is the closest prior art, den Broeder teaches a dose titration clinical trial of the D2E7 anti-TNFα antibody in which rheumatoid arthritis patients were effectively treated with a dose of 0.25 mg/kg/2-4 weeks.

While den Broeder teaches their trial was not designed to include anti-TNFα antibody dose steps smaller than 0.25 mg/kg, den Broeder further teaches that the anti-TNFα antibody dosage could be even further reduced in light of the absence of any disease flare-ups in the patients treated with 0.25 mg/kg D2E7 every 2-4 weeks. Furthermore, den Broeder teaches that even lower dosages are "supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNF-α antibody, documented for both D2E7 (up to 14 weeks EULAR response) and infliximab (up to approximately 18 weeks Paulus 20 response)." (see den Broeder, in particular Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

Converting the 0.25 mg/kg/2-4 weeks dosage of den Broeder to a per week basis gives 0.0625 – 0.125 mg/kg/week, which overlaps the claimed dosage range of 0.01 to 0.1 mg/kg.

Thus, based on the teachings of den Broeder the ability to treat rheumatoid arthritis with a dose of 0.01 to 0.1 mg/kg anti-TNFα antibody was expected.

Indeed, treatment of rheumatoid arthritis patients via the claimed methods was entirely obvious when the teachings of Stephens, Salfeld and den Broeder are considered in combination.

The den Broeder Reference

With respect to the den Broeder reference, applicant argues den Broeder is deficient because it teaches that the median of the calculated weekly dose was 32.5 mg/week, which applicant notes is the equivalent of 0.36 mg/kg/week for a 90 kg person.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

Applicant points to the median dosage result which falls outside of the claimed range, but fails to address that, according to den Broeder, while their clinical trial was not designed to include anti-TNFα antibody dose steps smaller than 0.25 mg/kg, the anti-TNFα antibody dosage could be even further reduced, especially for those three patients who did not have a disease flare-up after treatment with 0.25 mg/kg D2E7 every 2-4 weeks.

Moreover, applicant has not addressed that conversion of the 0.25 mg/kg dosage of den Broeder to a per week basis gives 0.0625 – 0.125 mg/kg/week, which overlaps the claimed dosage range of 0.01 to 0.1 mg/kg.

Furthermore, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Indeed, treatment of rheumatoid arthritis patients via the claimed methods was entirely obvious when the teachings of Stephens, Salfeld and den Broeder are considered in combination.

In addition, applicant argues den Broeder teaches away from the claimed invention in that of the 21 patients treated, 18 had a disease flair before reaching a D2E7 anti-TNFα dose of 0.25 mg/kg/2-4 weeks. Therefore, applicant concludes that "[o]ne of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success, based on the disclosure of den Broeder *et al.*, to treat with doses lower than 0.25 mg/kg, since only a small percentage of patients (i.e., 3 out of 21) were observed to reach the dose of *0.25 mg/kg* before exhibiting a flare in disease."

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

Given that den Broeder has shown in a clinical trial that a subset of rheumatoid arthritis patients can be successfully treated with a dosage of D2E7 anti-TNFα that on a per week basis (i.e., 0.0625 – 0.125 mg/kg) overlaps the claimed dosage range (i.e., 0.01 – 0.1 mg/kg), and given that anti-TNFα dose titration and the monitoring of response, for example, by monitoring disease flare up is a results effective variable routinely optimized by one of ordinary skill in the art as taught by den Broeder and Salfeld, the reference teachings provide a reasonable expectation of success to practice the claimed invention.

Moreover, it should further be noted that given the teaching of den Broeder, one of ordinary skill in the art would have been motivated to treat rheumatoid arthritis with the *lowest possible effective dose* of anti-TNFα antibody in order to minimize the risk associated with TNFα suppression and minimize treatment costs (which is also emphasized by den Broeder, see Introduction at page 638-639). It is noted that the teachings of den Broeder regarding anti-TNFα antibody dose titration are consistent with the teachings of Salfeld that anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions".

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Accordingly, the instant claims are unpatentable over Stephens in view of Salfeld and den Broeder.

It is noted that the functional properties of the anti-TNFα antibody (e.g. as recited in claim 41) are physical properties of the D2E7 antibody taught by Salfeld et al. It is further noted that treatment of specific symptoms of rheumatoid arthritis (e.g. as recited in claim 43) would necessarily be treated when treating rheumatoid arthritis as taught by Salfeld et al.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 are rejected/provisionally rejected, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

A. claims 1–7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69 and 70 of U.S. Patent No. 6,509,015;

B. claims 1-10 of U.S. Patent No. 7,223,394; and

C. claims 15-17 and 19 of copending application USSN 11/233,252.

each in view of Salfeld et al. (US Patent No. 6,258,562) and den Broeder (Rheumatology (Oxford). 2002 Jun;41(6):638-42)(see entire documents).

Note that this is a New Grounds of Rejection necessitated by applicant's amendment to the claims as well as the issuance of U.S. Patent No. 7,223,394 based on previous copending 09/801,185.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As a preliminary matter, it is noted that the elected species of disease under examination is "rheumatoid arthritis"; however, certain claims of U.S. Patent No. 6,509,015, and copending Applications USSN 11/233,252 and USSN 09/801,185, reading on other species of arthritic diseases are also included in this rejection because they anticipate the instant claims drawn to the a method of treating the genus of arthritic diseases.

Claims 1–7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69 and 70 of U.S. Patent No. 6,509,015 are directed to a method of treating various forms of arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The patent clarifies, e.g. in columns 2-3 bridging paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.
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Claims 1-10 of U.S. Patent No. 7,223,394 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The specification clarifies e.g. on page 3, 3rd paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Claims 15-17 and 19 of copending Application USSN 11/233,252 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The specification clarifies e.g. on page 3, 2nd paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in U.S. Patent Nos. 6,509,015 and 7,223,394 and copending application USSN 11/233,252 as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in the previous Office Action of February 8, 2007 and for the reasons put forth in the 35 U.S.C. § 102(b) and 103(a) rejections given above, the reference claims, in view of the teachings of Salfeld and den Broeder, render the claimed invention obvious.

With respect to applicant's argument that the instant claims are not obvious over U.S. Patent No. 6,509,015 in view of Salfeld and den Broeder, applicant's arguments are not found convincing for substantially the same reasons put forth in the 35 U.S.C. § 102(b) and 103(a) rejections given above.

With respect to applicant's contention that the provisional double patenting rejection over copending USSNs 11/233,252 and 09/801,185 (now U.S. Patent No. 7,223,394) will be addressed in these applications as neither is yet patented, Applicant's contention is acknowledged, however Applicant is advised that the instant rejection will be maintained until such time as a terminal disclaimer signed by the assignee and fully compliant with 37 CFR 3.73(b) is submitted.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
July 23, 2007

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

7/24/07